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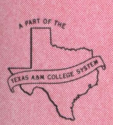
Biochemical and Fundamental Physiological Bases of Genetically Variable Growth of Animals



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Biochemical and Fundamental Physiological Bases of Genetically Variable Growth of Animals

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Growth is more than an increase in size. It is highly complex, the result of a heterogeneous array of processes of diverse kinds. The term "growth" itself is without consistent meaning and may refer to any or all of these: reproduction, increase in dimensions, linear increase, gain in weight, cell division, cell expansion, cell migration, protein synthesis and also fattening. Regardless of the connotation that the term may have, experience and experiment have long made it obvious that growth processes are highly plastic, responding to numerous forces, genetic as well as environmental.

Man has made much use of the genetic plasticity in patterns of growth to produce a variety of kinds and breeds of animals to meet man's fancy or economic purpose. Dogs of varied sizes have been bred to hunt and guard, to be seen and touched and admired. Horses of divergent sizes have provided power, speed and transportation for the small child and man. Animals have been selected for continuing improvement in the conversion of forage and grain into meat. The efforts of animal breeders, especially those of animals of economic importance, have never been greater than at present.

The ability to modify and control genetic diversity in growth requires more than knowledge of the relative importance of heredity and environment (Dickerson, 1954). Dickerson described growth as a process influenced constantly and directly by gene products within the cell and, later, by hormones, cell nutrition and morphogenic agents, each of which is controlled by interacting chains of gene-launched reactions that are subject to environmental modification. There is need for information concerning the modification of individual genic effects by other allelic and nonallelic genes and by the environment. There is need also for the appreciation of the effects of "growth" genes on other biologic processes. Maximum progress in breeding for superior growth in animals of economic importance may then depend upon the eventual elucidation of the physiological and morphogenetic bases for genetically variable growth.

STATISTICAL ANALYSES OF GROWTH PATTERNS

For statistical purposes, growth is most easily visualized, though inadequately, as the gain in total body mass. Typical mammalian and avian growth curves describing total growth are initially concave or exponential. The curve changes through a relatively straight and steeply ascending phase into an increasing convexity until it levels off as a straight horizontal line. The curve thus assumes an overall S-shape (Brody, 1945). Although a universal simple growth equation has not been devised, nor is one likely to be devised (Medewar, 1945), algebraic expressions of certain phases of the statistical continuity of growth can make the growth curve amenable to physiological analysis.

Much of the work in analysis of growth of animals has been limited to a consideration of the finite or average absolute rate of body gain:

$$\text{Average absolute rate of gain} = \frac{W_2 - W_1}{t_2 - t_1} = \frac{\text{second less first weight}}{\text{time elapsed between weighings}} \quad (1)$$

Although estimates based upon finite rates of growth, particularly during the straight portion of the curve, have provided a large and useful body of data, the finite estimation of growth is physiologically unsatisfactory. The times t_1 and t_2 are arbitrary and are not equivalent physiologically for the successive phases of development (Brody, 1945). Nutritional and other environmental forces also can markedly distort the time relationships in the growth process.

Animal growth can be considered a result of a counteraction of synthesis and destruction, of anabolism and catabolism of cellular materials of the body (Putter, 1920). Growth occurs so long as building-up processes prevail over breaking-down, and the animal reaches a steady state when both processes are equal. Bertalanffy (1957) attempted to described the statistical instantaneous rate of growth in terms of anabolism and catabolism:

$$\frac{dW}{dt} = aW^m - cW^n \quad (2)$$

The change of body weight is given by the difference in building up and breaking down; a and c are coefficients of anabolism and catabolism, respectively, and the exponents m and n are powers of the body weight W.[1]

[1]W, in these equations, also might appropriately represent a tissue, organ or body dimension.

The equation implies that the gross result of synthentic and degradative processes, not withstanding the complexities of such processes, can be expressed as a function of the body mass. The justification for such an assumption is based upon the fact that, at least in first approximation, the rate of all physiological processes heretofore investigated can be expressed in allometric or heterogonic formulas (Adolph, 1949). The intrinsic complexity of a phenomenon does not preclude it from following a simple, general law.

Allometric equations are based upon the concept that any physiological occurrence is kinetically related to the quantity of the *existent tissue mass*. That the existent tissue mass is dynamic, undergoing catabolism as well as anabolism, is indicated by the high order of biochemical turnover occurring in all tissues (Schoenheimer, 1947) and the high rate renewal of cells found in many tissues and organs of animals (Leblond and Walker, 1956).

Growth of mammals is not continuous and, therefore, a single set of values or constants for a species cannot be adequate for the entire period of growth. For example, during prenatal growth and early postnatal development, the body weight increases exponentially indicating that both m and n of equation 2 are equal to or approaching unity (Bertalanffy, 1941). At a point, generally preceding puberty, where the growth curve is inflective, the apparent value of m becomes less than unity while n may not deviate greatly from unity ($m<n=1$). The growth rate decreases until the steady state (mature weight) is reached and net growth ceases to occur.

Brody (1945) and his collaborators and students arrived at essentially similar conclusions following studies of body and organ growth of species ranging in size from the canary to the elephant. Brody suggested that the exponential growth may be represented by the equation:

$$\frac{dW}{dt} = k_1 W, \qquad (3)$$

an equation which may be derived from the von Bertalanffy equation (equation 1, $m = 1$, $n = 1$):

$$\frac{dW}{dt} = (a - c)\ W. \qquad (4)$$

Brody (1945) considered the growth during latter phases of development as being a function of the growth yet to be made:

$$\frac{dW}{dt} = -k_2\ (A - W) \qquad (5)$$

where A is the mature weight of the animal.

Equation 5, like the von Bertalanffy allometric equation when $m < 1$, recognizes the progressive diminution of growth rate as the animal approaches maturity. While the Brody equation states the final limiting factor of growth is the inherent mature size, however this may be controlled, the allometric equation emphasized the metabolic approach to a steady state.

Whether either of these equations or some other, perhaps yet to be devised, is the more appropriate remains to be determined. Both equations have an apparent validity in defining the parameters of growth (Putter, 1920; Bertalanffy, 1941; Brody, 1945). Both equations represent growth rate as a condition of the growing system, within a given set of environmental circumstances, rather than as an explicit function of time or age.

NATURE OF GENETIC VARIATIONS IN GROWTH PATTERNS

The uncontrolled variations in nutrition, temperature, humidity, infections by pathogenic organisms or parasites, and injuries have a larger influence than genetic variations in growth (Dickerson, 1954). Nonetheless, real genetic influences have been discovered and provide significant opportunities for breeding for variable growth.

The genetic variability in overall growth includes the simply inherited large differences such as lethals, dwarfism and other innate abnormalities, as well as the more useful variation arising from a multiplicity of genes with small individual effects (Dickerson, 1954). The large and easily recognizable differences are interesting in the academic sense and, as in the cases of recessive dwarfism in cattle (Crew, 1923; Lush, 1930; Baker *et al.*, 1950; Johnson *et al.*, 1950; Baker *et al.*, 1951), they may be a real problem in a breeding program. Yet these large differences, being negative, are seldom helpful in breeding animals for improved performance.

Brody (1945) concluded that the value of A (mature weight) and of the slope, k_2, of the postnatal growth curve (equation 5) are intrinsic or genetic characteristics of the species under given environmental conditions. The evidence indicates also that the mature weight, A, of individuals within species is a multifactorial hereditary characteristic. Large multigenic differences in animal size have developed under apparent conditions of natural selection as in the case of the large and smaller breeds of rabbits (Castle, 1922). Similar large differences in mature body size have been elicited by deliberate selection of mice (MacArthur, 1949) and of swine (Zeller, 1940).

With the exception of such large differences as previously noted, genetic variations in growth within an interbreeding population form a continuous series and often are confounded by environmental influences. Thus such genetic variations have been and are being evaluated by statistical techniques (Wein-

berg, 1910; Fischer, 1918; Wright, 1935; Lush, 1948; Bogart, 1959). Though most of the statistical determinations of the genetic components of variance of growth have been based on the average absolute rates of growth,

$$\frac{W_2 - W_1}{t_2 - t_1}$$

or of the weights at specific times (birth weights, weaning weights, etc.) instead of growth curve values or constants, they provide clear evidence that multigenic hereditary differences result in differences in rates of growth.

The work concerning the estimation of heritability of growth characteristics in beef cattle, sheep and swine has been reviewed by Warwick (1958), Terrill (1958) and Craft (1958). Table 1 is derived from the citations and summaries in these reviews plus pertinent additional reports. The magnitudes of the approximate average estimates of heritability (Table 1) indicate that birth weight, growth from birth to weaning, post-weaning growth and the efficiencies of feed utilization of cattle and sheep are high enough to permit useful selection for improved performance. Although the estimates of heritability of similar characteristics of swine generally are lower than of cattle and sheep, these estimates also are important.

Genetic influences on the growth of animals probably are expressed early in embryonic development. As an example, Gregory and Castle (1931) noted differences in the rates of cell divisions of large and small races of rabbits as soon as 48 hours after fertilization. Blunn and Gregory (1942) noted indications in the chick for the expressions of inherited growth differences at all stages of development which were measured. However, heritable maternal influences (Wright, 1922; Walton and Hammond, 1938; MacArthur, 1949; Venge, 1950), maternal environment, maternal age and parity, uterine nutrition, uterine space, litter size and gestation length in mammals (Krider *et al.*, 1946; Dickinson, 1960) and egg size in poultry (Shoffner and Sloan, 1948) generally mask much of the early influence of the individual genotype. Among the species tested, the genotypes of embryos on only sheep and cattle have an important influence on birth weight (Table 1).

Maternal influences might be expected to be transitory after birth, and post-natal compensatory growth has been observed in guinea pigs (McKeown and MacMahon, 1956), in cattle (Dickinson, 1960) and in sheep (Hunter, 1956). But in lactating species, the inherited growth impulse often is overshadowed by heritatble differences in milk production of the dam (Wright, 1922; Dickerson and Grimes, 1947; Drewry, Brown and Honea, 1959). The genotype of the dam is more important than the genotype of the pig from birth to weaning. Although about 30 percent of the variance in weaning weights of calves appears the result of the genotype of the calf (Table 1), part of this heritability is due to the inherited differences in birth weight (Gregory *et al.*, 1950). Gains in calves during the suckling period are largely under environmental rather than genetic influence. A similar statement may be made concerning sheep (Hazel and Terrill, 1943, 1945, 1946; Nelson and Ven Katachalan, 1949; Karam *et al.*, 1953).

As the animal gets older, the individual's own genotype exerts a steadily increasing influence on growth. This diminution of environmental and maternal effects and augmentation of genetic effects has been demonstrated in cattle (Knapp and Clark, 1947; Blackmore *et al.*, 1958), and in sheep (Harrington *et al.*, 1958), but to a lesser extent in swine (Craft, 1958) and in laboratory animals (MacArthur, 1949).

Dickinson (1960) proposed a model of mammalian growth in which an inherent or "genetic growth competence" controlled the total growth of the organism, but when nutrients and other environmental conditions are good, the animal takes temporary advantage of the conditions. The ability of an animal, for example, to fatten or otherwise to take temporary advantage of environmental variations which exceed the minimum demanded by the genotype for stable development is termed the "juvenile growth component." The juvenile growth component thus may obscure the genetic growth competence until maturity is reached. Genetic variance present in the juvenile component is considered to be unrelated to that in the growth competence.

The cumulative data suggests that though environmental and maternal influences often mask the interrelationships, a continuity of genetic variations in growth does exist from pre-natal development to mature weight. The birth weight-mature weight

TABLE 1. ESTIMATES OF HERITABILITY OF GROWTH CHARACTERISTICS OF CATTLE, SHEEP AND SWINE

Character	Species	Range, %	Approximate average, %
Pre-natal growth (birth weight)	Cattle	11-100	41
	Sheep	15- 72	32
Weaning weight	Cattle	—13-100	30
	Sheep	15- 56	33
	Swine (litter wt.)	3- 37	17
Post-weaning growth (absolute)			
Feedlot:	Cattle	19- 70	45
	Sheep	58, 84[1]	71[1]
	Swine	14- 58	29
Pasture:	Cattle	7- 43	29
Efficiency of feed utilization	Cattle	3- 99	46
	Sheep	15[2]	15[2]
	Swine	8- 72	31

[1]Two estimates only.
[2]One estimate only.

correlation in cattle has been reported as 0.33 and 0.41 (Matthews and Forman, 1954). Hammond (1932) recorded that the coefficient of correlation between weight of sheep at 1 week and at 61 weeks was 0.303 ± 0.201 for singles and 0.488 ± 0.079 for twins. Donald and McLean (1935) calculated a correlation of 0.50 between birth and 70-day weights of lambs. Cadmus (1949) found a similar relationship. Several workers (Dahmen and Bogart, 1952; Pierce *et al.*, 1954; Koch and Clark, 1955) found no relation between suckling and post-weaning gains of cattle, but Cartwright and Warwick (1955) reported significant correlations of 0.25 to 0.31 among birth weight, weaning weight and feedlot gain. Carter and Kincaid (1959) reported the genetic correlation between weight of steers at 6 months and feedlot gain was 0.69 and between the weight of heifers at 6 months and yearling gain on pasture to be 0.51. Such genetic continuity, if real, may prove to be more evident in the basic physiology of an animal than in the gross expression of growth.

MORPHOLOGIC VARIATION AND GROWTH RATE

The size and shape that any animal attains is the result of the coordinated growth of its parts. The growing mammal changes its form with increasing weight, probably as an inherent regulator to maintain biophysical homeostasis (Brody, 1945). As the animal grows, most of the vital organs, including brain, liver, heart, skin and cardio-respiratory system, tend to become a smaller portion of the body weight. Certain other parts, such as the muscular system, the mammary glands of the dairy animal and the digestive tract of ruminants, tend to become relatively larger parts of the whole.

Inasmuch as dimensional change must occur with increasing size (Thompson, 1941), some morphogenetic attributes likely are associated with that part of growth directed by the ultimate size of an animal. To maintain a fairly constant weight load, for example, the thickness of a bone should be proportional to the 3/2 power of a linear dimension of the body height, width or length. The animal which grows the faster, and thereby attains a heavier mature size, should be one that develops a thicker bone.

In several instances, increased body size appears the result of intrinsic dimensional change. Eaton (1939) noted that inbred lines of guinea pigs, differing markedly in mature size, had a larger amount of the soft tissues. Selection for body weight in mice (MacArthur and Chiasson, 1945) increased fleshing and obesity more than skeleton, and body length more than length of ears, feet or tail. Several workers (Dickerson, 1947; and Blunn and Baker, 1947) noted that the rates of gain of swine were correlated positively with fat and muscle content of the carcass and negatively with length of legs. Cummings and Winters (1951), however, noted that certain breeding groups of swine which gained the most rapidly were the least fat.

"Type" or conformation scores and body measurements have been used in attempts to correlate morphological variation in animals of economic importance. The characteristics thus far emphasized in cattle have been inefficient as predictors of growth rates (Black, Knapp and Cook, 1938; MacDonald and Bogart, 1954; Kidwell *et al.*, 1959), although certain relationships were found to be of statistical significance in some of the studies. Lush (1932) reported a tendency for animals long in body, tall in withers, small in flank girth, large in paunch girth and with narrow loins to gain the faster. Kohli *et al.*, (1957) noted, however, that steers which were shorter in height and in length of body and smaller in circumference of fore-flank were slightly superior in rate and economy of gain.

At present, the relationships between the qualitative aspects of body form to the genetic variation in rates and extents of growth thus lack definition. This is as might be expected since genetic factors controlling growth of particular portions or tissues (*e.g.* bone) of the body often obscure the variations associated with general size factors (Wright, 1932; Swain, 1945; Kidwell, Gregory and Guilbert, 1952). As Dickerson (1954) noted, one has only to observe the many sizes and shapes of dogs and of men to reach a similar conclusion.

On the basis of prima-facie evidence, it appears unlikely that one is able to select animals for improved rate of growth by selection for a certain body conformation, but the rate at which an animal approaches maturity may be related to body structure. This interesting possibility was suggested by Patrushev in 1940 to exist within breeds of cattle but, at present, remains untested and unverified. Patrushev suggested that, among cattle, microeurysomal individuals – which at maturity have the minimum height at the shoulders and maximum relative width, girth and length – tend to be the more rapidly maturing cattle, reaching their maximum development at earlier ages. The leptosomal cows which have relatively small girth, thin bones and light weight, are of a type associated with retarded development. The macroeurysomes have an intermediate growth precocity. Patrushev held the opinion that within the limits of a breed there are gradations of several morphophysiological types and these types should form the bases for selection of animals as to the elements of precocity. Unsubstantiated as Patrushev's hypothesis may be, osteodystrophic ("snorter") dwarf and comprest Hereford cattle, both microeurysomal types, tend to reach maturity at an age earlier than do their normal size counterparts. One may note also the small head, legs and bones of the early maturing meat types such as some Angus cattle, the Southdown sheep and the Berkshire pigs of the late 1940's (Hammond, 1951).

Pertinent to a concept that morphology is related to the rate of maturation, but not necessarily to the rate of juvenile gain in weight, may be Dickinson's

(1960) hypothesis of mammalian growth which included the terms, *genetic growth competence* and *juvenile growth potential.* The genetic growth competence is defined as that characteristic of a tissue, organ or body dimension which controls the level of nutrients needed primarily for maintenance of tissues already formed and secondarily for further growth. This component not only represents the competitive status of the character when nutrients are in short supply, but it also will control the mature size and shape. Growth of a character will cease when its metabolic potential is only sufficient to maintain the tissue mass already formed. When nutrients and other environmental conditions are good, variance in the genetic growth competence may be obscured, until maturity is reached, due to other factors influencing the utilization of nutrients in excess of the genetically controlled basic requirements, that is the so-termed "juvenile growth component."

Recent evidence indicates that morphophysiological relationships to growth patterns may be evident in a fine sense, such as in the development of epithelial structure. Turner (1959) noted that the genetic correlation between the body weight of sheep and the amount of wool per unit of body weight is significantly negative.

Sinclair and Kunkel (1959) noted that lambs which gained well under feedlot conditions also had greater development of the mucosæ of the rumen. The length of the papillæ appeared to be the criterion most closely related to previous rate of gain. Papillary development in the rumen seems to be dependent upon exposure to an environment of active microbial fermentation within the rumen (Sanders, Warner and Loosli, 1959). The active absorption of the products of microbial fermentation, the volatile fatty acids, from the rumen may in turn depend upon adequate papillary development (Martin *et al.,* 1959). The variation in ruminal development observed in feedlot lambs appears to be a structural expression of the previous rate of gain and possibly of the capacity for growth as it is affected by the general nutritional state, the inherent growth impulse of the animal, the ability of the animal to adapt to a functional symbiosis, and/or the active fermentation mass within the rumen.

Final evaluation of the fundamental physiological changes occurring with genetically variable growth may rest extensively upon knowledge of morphophysiological relationships. The present inability to correlate efficiently the morphology of an animal with its rate of growth may be only an expression of the insufficiency of that knowledge. Structure and function must be considered as coordinate and interrelated aspects of biological development (Carrel, 1931; Patrushev, 1940; Brody, 1945). An animal may exhibit a characteristic of superior growth as a result, for example, of augmented growth of all parts of the body, of a greater development of muscle without extensive skeletal change or of improved ability to fatten. The metabolic pattern supporting each kind of improved growth is likely different from the other.

PHYSIOLOGIC BASES FOR VARYING CAPACITIES OF GROWTH

Although the physiology of gene action has received extensive study and review (Wright, 1945; Wagner and Mitchell, 1955; McElroy and Glass., Eds., 1957), existing data do not yet lead to a workable model for the genic control of growth. Search of the literature provides explanation in specific metabolic terms for only a few of the inherited large differences in growth, and these explanations are inadequate. The accumulated experimental data, however, do indicate that all gene functions are executed by chemical means. Thus each phenotypic expression of genic differences, including growth, must have an intermediate metabolic basis.

Nutritional Requirements

Hammond (1951) pointed out that there exists between the different tissues and parts of the animal body a graded series of priorities for any nutrients which are available. If the plane of nutrition is very high, all tissues are served to their maximum requirements. When the plane of nutrition is lowered, fat ceases to be put on, but the other tissues continue growing, though at a lower rate. When the plane of nutrition is lowered still further, bone and brain continue to grow, but at a much slower rate, muscle ceases to grow and fat is withdrawn to supply energy for such growth as continues.

It is clear that the expression of inherited growth potential and the nutrition of the animal are greatly interdependent. An example of such interdependence exists in the recent findings of Wagnon and Rollins (1959) who estimated the heritability of weight at 600 days of age to be 0.44 for heifers which were supplemented to promote continuous growth during fall and winter. The estimate was —0.19 for heifers which were not supplemented and lost weight during the winter, but made good gains during a subsequent period of good pasture. Morley (1956) noted that heritability of body weight of sheep at 12 months was 0.29 on a low plane of nutrition and 0.36 on a high plane, but at 17 months the correlation was 0.40 on the low environmental plane and 0.26 on the high.

The efficiency of feed utilization decreases generally with age and increasing body size. There are, however, significant variations from the regression of feed efficiency on body size (Carter and Kincaid, 1959a; Table 1) which indicate that the ability to utilize nutrients efficiently is a heritable characteristic. Several investigators (Winters and McMahon, 1933; Black and Knapp, 1936; Knapp *et al.,* 1941; Stanley and McCall, 1945; Kohli *et al.,* 1951; Carter and Kincaid, 1959b) also have noted a high positive

correlation between rate and efficiency of gain in cattle, especially when efficiency is adjusted for differences in body weight. The factors resulting in improved efficiency in utilization of food thus may be those affecting superior growth. Similar positive relationships between greater efficiency of nutrient usage and rate of growth or fattening have been noted in chickens (Hess and Jull, 1948), in laboratory animals (Palmer *et al.,* 1946; Dickerson and Gowen, 1947) and in swine (Dickerson, 1947; Krider *et al.,* 1946).[2]

It seems highly probable that naturally existent genetic variation in requirements for specific nutrients, such as those induced by mutagenic agents in *Neurospora* (Beadle and Tatum, 1941) and in bacteria (Lederberg and Tatum, 1946), are sources of heritable variation in the growth of animals. Genetic differences have been reported with respect to differential times of survival of inbred lines of rats fed a rachitic diet (Gowen, 1936). Differences have been noted with respect to severity of effects of vitamin D insufficiency in various breeds of swine (Johnson and Palmer, 1939) and in creeper chickens (Landauer, 1934). Certain breeds of chickens were noted to utilize thiamin more efficiently than others (Scrimshaw *et al.,* 1945). Genetic differences in requirements for riboflavin have been noted to occur in mice (Fenton and Cowgill, 1947) and in chickens (Lamoreux and Hutt, 1948). Marked differences in growth, mortality and "goose-stepping" were noted among certain inbred strains and their crosses in swine when a diet deficient in pantothenic acid was fed (Gregory and Dickerson, 1952).

The relatively limited observations on inheritance of nutritional requirements of animals are thus in line with the expectation based on studies with microorganisms. Such genetic effects might be alleviated by nutritional means by supplying the nutrient in either adequate or excess amounts; therefore, the hereditary increased requirement for a nutrient may be hidden in animals receiving a high plane of nutrition. However, it is well known that some metabolites become inhibitory in high concentrations. In the lower organisms, some mutations greatly increase the sensitivity of the mutant strain to inhibition by normal metabolites (Wagner and Mitchell, 1955). Perhaps some of the greater genetic variations in growth of animals actually observed under the higher planes of nutrition are the result of sensitivities to an imbalance in a plethora of nutrients.

Capacity for digestion of feedstuffs may be part of the genetic and environmental complex controlling the growth of animals. Craft and Willham (1956) found that certain inbred pigs had reduced capacity to digest feed, particularly the protein and nitrogen-free extract. Baker *et al.,* (1951) noted that, while digestive capacities could not account for the large variation in abilities to make gains, the more efficient beef cattle digested the crude fiber of the ration more effectively than the less efficient animals. The recently discovered relationship of ruminal development and state of health of rumen tissues to rate of gain in lambs (Sinclair and Kunkel, 1959; Kunkel *et al.,* 1959) may be reflected in a similar variation in capacities for digestion of cellulosic feeds. The effect of variation in capacity for feed consumption or in appetite upon growth has not been evaluated.

Endocrine Physiology

Much data are available showing that experimental alteration of the hormone balance markedly affects the pattern of animal growth. The secretions of the adenohypophysis (anterior pituitary), the thyroid, the adrenals and the gonads have all been shown experimentally to alter the growth of animals (*cf.,* Pincus and Thimann, Eds., 1955). It logically follows then that intrinsic differences in endocrine physiology mediate deviations in growth and development.

Some simply inherited large differences have been related to endocrine disfunction. Mouse dwarfism, first described by Snell (1929) to be inherited as a simple recessive, was found to be associated with thyroids and adrenals of reduced size and deranged structure (Smith and MacDowell, 1930, 1931). The anterior pituitaries of the dwarf mice lack the growth hormone, but have a high concentration of gonad stimulating hormone. Acidophilic cells are absent (deBeer and Gruneberg, 1940). Pituitary involvement has been suggested to occur in dwarf rabbits (Castle, 1940; Green, 1940) and in dwarf guinea pigs (Sollas, 1914). Bogart and Dyer (1942) described dwarf lambs with the short legs, thick shoulders and bulging forehead indicative of thyroid insufficiency. Histological study of the thyroid showed it to be abnormal. Dwarfism due to an inherited thyroid hypofunction was reported by Landauer (1929) and by Mayhew and Upp (1932) to occur in the chick.

Relatively recent evidence has suggested endocrine mediation also of part of the variation of growth resulting from multiple systems of genes. Using two genetically different lines of swine selected for rapid and slow rates of gain, Baird *et al.* (1952) demonstrated that the adenohypophyses from "rapid-line" pigs contained significantly greater amounts of growth

[2]**Feed efficiency in most of the investigations cited here is expressed in terms of food or feed required to produce a unit of body gain. The assumption is that the more efficient animals utilize nutrients for making gains in proteins, minerals and/or lipides over and above the body constituents gained had the animals been less efficient. Studies with laboratory animals support such assumption (Palmer *et al.,* 1946; Dickerson and Gowen, 1947). However, one unit weight of fatty tissue contains the caloric equivalent on the order of five or more unit weights of the balance of the nonosseous tissue of the animal body. Thus it is possible that an animal may utilize the caloric content of the food more efficiently than another animal of the same species and yet gain less weight as a result of a metabolism extremely directed toward fat synthesis. The genetically obese mice studied by Mayer (1955) may be an example.**

hormone than did the same quantity of tissue from the "slow-line." These workers suggested that the larger amount of growth hormone secreted by the "rapid-line" pigs accounted for the more rapid gains.

Smyth and Fox (1951) reported that the heavier-gaining turkey poults had higher rates of secretion of thyroxine. Elijah and Turner (1942) noted that faster-gaining larger types of swine had a higher thyrotropin output. Gawienowski *et al.* (1955) similarly measured higher levels of protein-bound iodine in the blood sera from faster-gaining gilts and barrows. Singh, Henneman and Reineke (1956) found that ewe lambs with higher rates of thyroid secretion, as measured by thyroid output "half-time," tended to gain more during a 30-day test period.

Results of preliminary studies with young beef cattle (Kunkel *et al.,* 1953a) suggested that the level of serum protein-bound iodine (PBI) could be related to rates of gain in the feedlot. The early data suggested that there is an optimum level of PBI associated with gains and feed efficiency. Further study involving more than 500 beef calves in gain evaluation tests (Kunkel *et al.,* 1957; Green, 1958) produced only little support for the original suggestion that the concentration of PBI in the serum will account for a significant amount of the variance in feedlot gain. However, a significant relationship between the serum PBI and the rate of gain of young cattle presently cannot be discredited.

Recent findings suggest that the physiological effectiveness and clinical interpretation of the PBI levels is dependent in part upon the level of serum globulins or the level of a fraction of the globulin. A wide variation in the circulating thyroxine, in human subjects, can occur as a result of a wide variation in the thyroxine-binding serum globulin (Albright *et al.,* 1955; Tanka and Starr, 1959). Noting the significant positive correlations between the levels of serum PBI, the serum protein fractions and the level of reduced glutathione in erythrocytes, Kunkel (1958) concluded that a similar physiological relationship existed in young cattle. It should be noted that the correlative variations in serum constituents and serum proteins are not limited to thyroxine. The concentrations of plasma estrogens and corticosteroids and serum copper in humans vary in direct relationship to variations in the respective binding proteins (Sandberg and Slaunwhite, 1959; Holmberg and Laurell, 1947).

Biochemical Variations

In the broad or gross sense, variations in the chemical composition of animals occur as the simple result of differential rates of growth of bone, soft tissues and muscle and of fattening (Eaton, 1939; MacArthur and Chiasson, 1945; Dickerson, 1947; Dickerson and Gowen, 1947; Cummings and Winters, 1951). An implication of heritable developmental variances in chemical constitution is that they are the result of metabolisms somehow different.

Putnam (1951) reported experimental results which suggest that heritable differences in growth rate of rats are due in part to the genetic determination of the rate of protein synthesis. Protein synthetic activity in liver slices was heritable, as indicated by strain differences, and appeared to be related with weaning weights of the strains but not with post-weaning growth rate. Lewis and Page (1956) compared the serum lipoprotein and cholesterol concentrations in "mesomorphic" and "ectomorphic" miniature swine fed the same diet and in which relative weight gains were similar. The "mesomorphic" or more obese pigs had higher concentrations of total serum proteins, albumin, cholesterol and β-lipoproteins. These findings are analogous to those of Mayer (1955) who noted that a genetically determined obesity in mice was associated with increased lipogenesis and cholesterolgenesis, a resultant hypercholesterolemia, and a hyperglycemia. Hereditary chondrodystrophy in chicken embryos is characterized by a shortening and curvature of the legs, a shortening of the base of the skull and a diminished glycine content of the embryo (Byerly *et al.,* 1933; Patton, 1937). In these instances, at least, genetic variations in growth and in gross composition are associated with quantitative differences in metabolic events.

Further support for the concept that biochemical patterns reflect patterns of growth has been obtained also in the studies of biophysical forces indirectly related to growth. The calculated relationships between the body weights of animals and the cytochrome oxidase activities of certain tissues suggest that the summated cytochrome oxidase activity of the body is nearly proportional to the size dependent basal metabolism in the mouse, rat, dog, sheep, swine and cattle series of animals (Kunkel *et al.,* 1956). A similar relationship may exist with respect to the cytochrome *c* concentrations of various epithelial tissues and the basal metabolic rate (Rosenthal and Drabkin, 1943). Patrushev (1940) interpreted his data to indicate a relationship between the concentration of blood glutathione and hemoglobin to the hereditary morpho-physiological status of cattle and horses. The faster-maturing, microeurysomal cattle had higher levels of blood glutathione at 3 years of age. Horses genetically adapted to racing had higher amounts of hemoglobin within their blood.

Prompted by the rational that metabolic differences associated with variable growth might be reflected in the balance of metabolites, several groups of workers have made numerous chemical and cytological determinations of blood and urine of cattle (Colby *et al.,* 1950; MacDonald *et al.,* 1956; Nelms, 1956; Williams, 1955; Alexander *et al.,* 1958; Price *et al.,* 1959; Arthaud *et al.,* 1959). Blood urea, uric acid, total non-protein nitrogen, amino acids, creatine, creatinine, cholesterol, glucose, hemoglobin, serum

proteins and fractions of serum proteins, sulfhydryl, hematocrit values and circulating erythocyte and eosinophile numbers have been estimated, but generally have been variably related to growth and only to a small extent. Significant relationships of interest, however, were noted in a few instances.

Coefficients of correlation between blood urea and subsequent rate of growth of young beef animals of -0.31 ($p<0.05$) and -0.51 were obtained by Price *et al.* (1959) and Colby *et al.* (1950), respectively. Price *et al.* (1959) also recorded the following coefficients of correlation: 0.38 ($p<0.01$) between blood urea and subsequent efficiency of feed utilization, -0.30 ($p<0.05$) and -0.35 ($p<0.05$) between blood uric acid and, respectively, subsequent and preceding gains and 0.37 ($p<0.01$) and 0.52 ($p<0.01$) between blood uric acid and, respectively, the subsequent and preceding efficiencies of feed utilization. Although the reported calculations of Price and co-workers are overall calculations and, unfortunately, do not account for the significant covariance resulting from breed and sex differences, their findings may be indicative of a greater use of amino acids in superior growth.

Arthaud *et al.* (1959) obtained, in one experiment with 43 bull calves, coefficients of correlation of 0.44 ($p<0.01$) and -0.41 ($p<0.01$) between the initial level of blood glucose and, respectively, the subsequent gains and efficiencies of feed utilization. After consideration of other data, however, these workers concluded that the relation of blood glucose to rate of growth is not consistent. Fluctuating nutrient consumption by the animal, variations and changes in blood volume, varying patterns of production and excretion and indeterminate metabolic relationships can affect the blood level of glucose and other metabolites. Yet the observed significant correlation between the levels of metabolites in blood and rates of growth under certain controlled conditions are additional evidence of the existence of metabolic bases for variability in patterns of growth.

The serum proteins of blood are products of cellular metabolism. Liver appears the major source of the serum proteins, but some specific proteins appear to have other sites of production. Serum alkaline phosphatase may be largely the product of osteogenic cells (Moog, 1946). Acid phosphatase is principally of liver and splenic origin. The γ-globulins are thought to arise from the reticuloendothelial system. Transaminase appears in the serum as a spillage from cellular contents in cardiac, hepatic, muscular and perhaps other tissue damage (Wroblewski, 1958). The major conclusion that one may draw from the aggregate of data on serum proteins is that the level of such proteins quantitatively and qualitatively reflect both function and disfunction, some of which must be related to growth.

Larson and Touchberry (1959) described the general changes in serum proteins occurring with age in dairy cattle. These workers recorded the high significant positive correlation between age and blo serum level in the bovine. The protein fracti associated with immune bodies were responsible the major increased serum protein level with a Their data also show an early diminution of th α-globulins up to about 1-1.5 years of age, and subsequent elevation.

Price *et al.* (1959) partitioned the serum protei of cattle by means of paper electrophoresis, but were unable to show the existence of any definite relation ship of the percentage of any protein fractio (albumin, α-globulin, β-globulin, or γ-globulin) a growth. However, preliminary data obtained b Green (1958) indicated that the chemically separate serum "globulin" and rate of gain were related sig nificantly in certain groups of Hereford and Angu cattle.

The concentration of serum alkaline phosphatase declines with age in several species of animals (Bodansky, 1934; Earle, 1952; Kunkel *et al.*, 1953b). The variation in serum alkaline phosphatase also appears to be, in part, heritable, as indicated by the higher levels in the Brahman breed of cattle, as contrasted with the enzyme level in European breeds (Kunkel *et al.*, 1953b), and by differences among inbred lines of chickens (Stutts *et al.*, 1957).

The relationship of serum alkaline phosphatase activities to rates of growth does not appear consistent. In a limited number of Hereford and Angus bulls, the correlation between the *initial* phosphatase level and subsequent feedlot gain was -0.19, and between *final* phosphatase activities and feedlot gain was -0.5 (Kunkel *et al.*, 1953b). In subsequent study with Brahman cattle, Fletcher *et al.* (1956) noted that the relationship of alkaline phosphatase activity and subsequent or contemporary gain was quite variable, but that most of the correlations were positive, and only positive correlations were significant statistically. Alexander *et al.* (1958) reported that the female Hereford and Angus calves in their experiments showed a consistent positive correlation between alkaline phosphatase activities and rates of gain. These workers suggested that sex differences exist, since bulls demonstrated variable and sometimes negative correlations. Combs *et al.* (1959) found that the 1 and 7-day phosphatase activities were not significantly related to weaning weights of 321 pigs, but the fact that milk production of the dam overshadows the inherent growth impulse of the pig (Dickerson and Grimes, 1947) should be reiterated. The relationship of the level of serum alkaline phosphatase and the intrinsic pattern of growth thus is yet to be delineated.

Attention has turned recently to another serum protein that may be determined as a specific entity, ceruloplasmin (Holmberg and Laurel, 1947). Ceruloplasmin is a copper-containing protein with electro-

phoretic mobility coincident with the α-globulins and can be identified chemically or from its oxidative activity. Analyses of data collected at the beginning of an experiment with eight 6-months-old female calves (Hereford and Angus) indicated a significant positive relationship between the level of the globulins and the ceruloplasmin (Deyoe, 1959). With increasing age, the relationship was altered. Over the entire period, however, the ceruloplasmin contents of the sera decreased with age while the total and component fractions of the globulins increased. Thus ceruloplasmin is a specific protein which follows a pattern of change distinctive from that of other serum α-globulins.

The possible significance of the changes in ceruloplasmin has recently become apparent. The data now available (Table 2) suggest a significant negative relationship between the level of ceruloplasmin and the concurrent rate of growth in both sheep and cattle under certain, but as yet undefined, conditions.

The tissue constituent that has received the most extensive and continuing study has been that of the sulfhydryl content. Sulfhydryl compounds, glutathione being the most important, have long been associated with cell proliferation and, hence, increasing size (Hammett, 1930; *cf.* Needham, 1942, pp. 420 ff). Gregory and Goss (1933a,b,c) related the concentration of glutathione within the newborn rabbit to the adult size. The total glutathione concentrations of Barred Plymouth Rock embryos were found to be slightly, but consistently, higher than concentrations found in White Leghorn embryos (Gregory *et al.*, 1935, 1936). Later Gregory and associates noted a similar difference among the 2 to 14-day-old chicks of these breeds. These results pointed to a breed difference in glutathione metabolism and suggested, as well, that the glutathione concentration of embryos was correlated with cell proliferation at 14 days of incubation, with growth rate after hatching and with adult weight.

Like the general process of growth itself, the accumulation of chemical constituents can be analyzed statistically by allometry or the differential growth ratio:

$$y = kW^b \qquad (6)$$

where y is the quantity of a chemical constituent, k a constant and b the allometric constant (Huxley, 1924; Needham, 1942, pp. 532 ff; Adolph, 1949). Lerner *et al.* (1936) subjected the earlier glutathione data of Gregory and Goss (1933c) to allometric analyses and differences in the allometric constant were found for the different breeds of rabbits. The larger breeds showed the larger allometric constant. Stutts and Kunkel (1958) subjected data from New Hampshire and White Leghorn embryos to allometric analyses and noted that in embryos weighing more than 10 gm. the rate of glutathione accretion was significantly greater in the embryos of the heavier New Hampshire breed.

Patrushev (1940) followed the characteristic changes – diminution after birth and subsequent elevation with age – in the concentration of glutathione in the bloods of various breeds of cattle. He concluded that the characteristic changes with age occurred at a younger age, and with more intense variation, in the smaller late-maturing breeds. Stutts and Kunkel (1958) noted in their interbreed comparison of the variations with age of the glutathione concentrations in chicken embryos that the highest concentration of glutathione per unit weight occurred on the 13th day of incubation in the New Hampshire embryos and on the 14th day in the White Leghorn embryos. The earlier appearance in the 13 to 14-day peak in glutathione concentration is perhaps predictive of a higher rate of growth and also of a higher level of glutathione in the blood of the mature bird. The findings of Gregory and co-workers, of Patrushev and of Stutts and Kunkel support a suggested pattern: the net synthesis of glutathione by the growing animal follows a variable pattern and both the pattern of glutathione synthesis and that of growth have, in part, a common genetic control.

That the level of glutathione within the blood or erythrocytes is characteristic of breed and individual has been verified in both young beef cattle (Kunkel *et al.*, 1954) and mature dairy cattle (Patterson, 1956). It also is a heritable characteristic of the mature chicken (Stutts *et al.*, 1956). At present, however, the data are insufficient to allow the interpretation of the level of blood or erythrocyte glutathione in terms of a propensity for superior growth.

TABLE 2. COEFFICIENTS OF CORRELATION BETWEEN SERUM OXIDASE ACTIVITY (CERULOPLASMIN) AND CONCURRENT RATES OF GAIN OF SHEEP AND CATTLE IN SUMMER FEEDING CONDITIONS

Species	Dietary treatment (daily addition)	Gain period, days	*n*	*r*
Sheep (wethers)	Basal[1]	28	10	—0.79**
	" + 2 mg. tetraalkyl-ammonium stearate	28	7	—0.63
	" + 15 mg. diallyl-stilbestrol	28	10	—0.09
	" + 15 mg. diallyl hexestrol	28	10	—0.61
	" + 15 mg. hexestrol	28	9	—0.84**
	" + 7 mg. hydroxyzine HCl	28	10	—0.82**
Cattle (steers)	Pasturage[2]	56	18	—0.49*

[1]Sorghum grain, soybean oil meal, cottonseed hull ration, self-fed.

[2]East Texas Pasture Investigations Laboratory, Lufkin, Texas.

*Significant statistically ($p<0.05$).

**Highly significant statistically ($p<0.01$).

Schultze (1955) found that blood sulfhydryl was related significantly to subsequent gain (r = −0.51) in very young dairy calves. Kidwell *et al.* (1957) calculated a correlation coefficient of −0.35 between the level of blood glutathione and subsequent rate of gain in post-weaning beef animals. Inspection of their data reveals that most of the differences in blood glutathione could be accounted for by variations in levels of the erythrocytes, which contain most of the glutathione found in blood. Arthaud *et al.* (1959) were unable to show a relationship between the level of blood sulfhydryl and rate of growth of post-weaning beef animals. Kunkel (1956) found significant curvilinear coefficients of correlation, ranging from 0.41 to 0.59 between the sulfhydryl-hemoglobin ratios to subsequent and contemporary rates of feedlot gain in Brahman, Charbray and Angus cattle (Table 3). The coefficients for Hereford and Santa Gertrudis cattle were small and non-significant. Matsumoto *et al.* (1958) reported that the genetic correlation between body weight of chicks at 20 days of age and the level of blood glutathione was −0.44, but again the glutathione concentration could be accounted by the variance in hemoglobin and, hence, in the level of erythrocytes.

Resistance to Disease

Though it is not the purpose of this review to dwell upon the effects of environment upon growth, iteration should be made that some variations in growth are likely mediated by genetically determined incompatibility with the environment. Such incompatibility elicits disease which may vary in effect from simple discomfiture and an almost imperceptible reduction in growth rate to a resultant death, the termination of all growth processes. It is not clear whether effective breeding programs can be devised to counteract specific diseases, particularly infective diseases (Bogart, 1959, pp. 336 ff; Hutt, 1958), in individual resistance or susceptibility to diseases may be part of the explanation of deviations in pattern of growth.

Genetic differences in the ability to resist various infectious diseases have been demonstrated among strains of mice (Gowen, 1948). These include infections by *Salmonella enteriditis, Salmonella typhimurium* (mouse typhoid) and *Bacillus piliformis* (piliformis disease), and such virus diseases as St. Louis encephalitis, pseudorabies and yellow fever. Cameron *et al.* (1943) found that resistance to brucellosis in swine can be inherited. Lambert *et al.* (1939) found evidence for inherited resistance to encephalomyelitis in horses. Part of the adaptability of certain breeds of cattle to unfavorable climates rests in resistance to ticks and other insects (Bonsma, 1951; Johnson and Bancroft, 1918) and thus to the diseases these insects may carry. Warwick *et al.* (1949) were able to select sheep and goats whose progeny proved better able to withstand infection by the worm *Hæmonchus contortus* than the unselected controls.

A molecular basis for disease resistance also is suggested. Rich (1923) found that guinea pigs more susceptible to hog cholera had a lack of blood complement. More recently certain humans who were highly susceptible to a number of infections were characterized as having agammaglobulinemia (Gitlin *et al.*, 1956). Such people are incapable of synthesis of part of the immune components of the serum proteins, the gamma-globulins.

It seems clear that genetic differences have much to do with the viability and health of animals. Disease resistance or susceptibility *per se,* however, is a characteristic not necessarily related to general vigor, growth rate or body size, but becomes a factor in growth only when the animal is challenged by a pathogenic or irritating agent. For example, Wright *et al.* (1921) found no relation of rate of gain or body size to the inherent resistance of guinea pigs to tuberculosis.

Altered metabolism may reduce rates of growth by reducing the efficiency with which nutrients can be utilized. In some instances, the metabolism may be so aberrant as to produce a defined physiogenic disease or to produce a specific sensitivity to the environment. Perhaps fortuitously, or as a result of incomplete study, recognized physiogenic diseases are largely those which afflict only the human being. One finds few counterparts in animals to the phenylpyruvic amentia, alcaptonuria, amaurotic idiocy, hypercholesterolemia and xanthomatoses, galactosemia, pentosuria and diabetes mellitus of human beings. Nonetheless, porphyria has been noted in cattle and swine. This condition, characterized by the accumulation of porphyrin in the blood, its deposition in bones, teeth and other tissues, and its excretion in the urine, is a simple recessive defect of

TABLE 3. COEFFICIENTS OF CURVILINEAR (QUADRATIC[1]) CORRELATION BETWEEN BLOOD SULFHYDRYL-HEMOBLOBIN RATIO AND SUBSEQUENT OR CONCOMITANT RATE OF FEEDLOT GAIN IN YOUNG BEEF CATTLE

Breed	Test year	Sex	*n*	R
Brahman	1954	Male	15	0.51
		Female	36	0.41*
	1955	Male	14	0.50
		Female	14	0.49
Charbray	1955	Female	28	0.53*
Angus	1956	Male	38	0.41*
		Female	31	0.45*
Hereford	1955	Male	67	0.18
Santa Gertrudis	1955	Female	14	0.23
	1956	Male	49	0.20

[1]Rate of gain $= k + a\left(\frac{SH}{Hb}\right) + b\left(\frac{SH}{Hb}\right)^2$

*Significant statistically ($p<0.05$).

metabolism (Fourie, 1953; Clare and Stephens, 1944). One effect of excessive porphyrin in the blood is to make animals extremely sensitive to sunlight and affected cattle exposed to sunlight develop severe abscesses in all parts of the body not covered by hair.

Hancock (1950) described a photosensitization found in Southdown sheep and caused by a simple recessive mutation. Lambs homozygous for this defect have a malfunction whereby they fail to excrete phylloerythrin, a product of the partial metabolism of chlorophyll. In defective lambs, phylloerythrin gets into the general circulation and in unprotected areas of skin it is activated by exposure to light. This condition is aggravated by the consumption of plant foods which contain the pigment.

Part of the individual's fitness or unfitness for an environment lies in the nutrition and nutritional requirements of the animal. This has been discussed previously. There is, in addition, the genetic compatability with the environment which includes the ability to cope with the physical elements of climate and weather, the ability to cope with competition and other assorted irritants, the resistance to infection by pathogens or parasites, and the absence of an aberrent metabolism which may result in a sensitivity to a specific element of the environment. Compatability with climate may be illustrated best by the superior performance of Zebu or Brahman cattle in areas of high ambient temperatures and humidity (Rhoad, 1938; Bonsma, 1951). Adaptability to unfavorable temperatures appears translatable to higher gains in hot weather, at least in interbreed comparisons (Cartwright, 1955). Physiological explanation for such differences in adaptation to unfavorable climates is largely lacking, but, in one instance, that of the higher heat tolerance of the White Leghorn chicken, lower mortality in hot weather seems to be associated with greater water consumption by that chicken (Fox, 1951).

Competition among animals has been a long recognized factor in the performance of animals. Crampton (1929) suggested that the more aggressive swine hand-fed as a group consume a disportionate amount of available feed. Individual-fed pigs gained more than those fed as a group. On the other hand, positive effects of group feeding steers were observed by Kidwell *et al.* (1954).

Subjective observations of animal groups indicate that most animal communities develop a sort of social hierarchy or "peck order" (Guhl, 1957; McBride, 1959) which may affect individual capacities for growth. The effects of heredity in establishing the community order or the pattern of competitive social behavior are undefined, but there can be but little doubt that aggressiveness and gumption, irritability and nervousness, and alertness and intelligence have in some part a genetic determination.

PRESENT OUTLOOK

The accumulated data force the present conclusion that the molecular biology underlying the varying patterns of growth is a highly complex metabolism. It might appear then, *a priori,* that efficient physiologic definition of a deviation in growth, would require consideration of an almost unworkable multiplicity of factors, but such may not prove a practical requirement.

Enough data are available to indicate that there are certain "crucial" or distinctive metabolic peculiarities which may be associated with either diminished or augmented growth. Glutathione is a case in point. Its synthesis in cells is associated with the mitotic process (Mazia, 1954). Its marked diminution in dying tissues or organisms is a result of dying processes; death is likely not the result of the diminution of tissue glutathione. Its net synthesis within living tissues is extensively under genic direction and there is evidence to suggest that the genic direction of net glutathione synthesis is, in part, a common direction of growth itself. Its relative pattern of net synthesis, at least in the chicken embryo, seems less affected by environment than by heredity. Yet the glutathione concentration, like growth, is affected and effected by multifarious metabolic and biochemical mechanisms. Other tissue constituents — serum phosphatases and similar proteins, tissue cytochromes, any of a number of substances within the cellular milieu — may prove to be substances with a critical, yet general, metabolic relationship to growth.

The interposing effects of environment or chronic disease may be manifested also by a metabolic distinctiveness. Ceruloplasmin in serum is elevated under the stresses of disease and pregnancy (Markowitz *et al.,* 1955). The serum ceruloplasmin level thus may be indicative of the adaptation of the animal to the stresses of a specific regimen. Similarly, elevated serum transaminase activities result from insult to any of a number of tissues and thus appear diagnostic of perhaps otherwise undetected injury (Wroblewski, 1958). There are likely other biochemical indices of hereditary and environmental interactions awaiting definition.

The emphasis in further attempts to accomplish a physiological and biochemical description of variable growth will remain the search for and the study of biochemical and/or morphogenetic changes which bear a decisive relationship to the course of growth. Success in such study doubtless will require the concomitant development of statistical and mathematical models with physiological validity to describe the continuity, or discontinuity, of growth as well as to account for the continuing change in the course of growth. Simple models based upon assumptive linearity and additivity of the varying factors in growth may prove inadequate, if not incorrect.

Progress in the research, as a matter of course, will require consideration of the discernible factors

of age, sex, heredity, nutrition and disease. Prior environment and previous nutrition of the animal also may affect the interpretations of any study of comparative biochemistry. Moreover, the conventional expressions of biochemical variations in terms of concentration within tissues or sera appear in several instances – *e.g.,* serum protein-bound iodine and corticosteroids – to have indeterminate physiological meaning. The proteins binding and hence possibly inactivating such serum constituents also may vary in concentration and, therefore, must be evaluated.

Though technical difficulties remain evident, there can be no doubt but that effective progress can be made toward substantive physiological explanations of differing patterns of growth. Such explanations can yield a working knowledge of the individual animal. From such explanations can come the indices predictive of the potential performance of an animal; but predictive indices may not be the most useful results from such research. From such explanations may come the most promising bases for the ultimate description of genetic interrelationships as applied to animal performance – the delineation of the chemistry of gene action within an animal organism.

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